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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,423	07/31/2003	Masaya Tohyama	59150-8023.US00	3705

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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 09/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/633,423	TOHYAMA ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,22,25-28 and 262-266* is/are pending in the application.

4a) Of the above claim(s) *24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,22,25-28 and 262-266* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *21-22,25-28,262-266* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/28/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's remarks and amendments filed 28 June 2006 have been entered. Claims 1 – 20, 23, and 29 – 262 are canceled; claims 263 – 266 are new.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

3. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 28 June 2006 has been entered.

Election/Restrictions

4. Claim 24 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 25 July 2005.

5. Claims 21 – 22, 25 – 28, and 263 – 266 are pending and under examination.

Information Disclosure Statement

6. The IDS filed 28 June 2006 has been considered. Note, however, that the reference by Chin has been crossed off. The text by Chin indicates that the accompanying sequences consist of every possible combination of nucleic acid bases in oligonucleotides of 8 to 12 bases in length with 40 to 60% GC content. It is not immediately obvious how this pertains to the instant invention, which is not directed to either 8- to 12-mers of nucleic acid, or to methods of administering them.

If applicant would like specific nucleic acid or amino acid sequences considered as prior art, applicant is invited to submit them. It would be helpful if a brief explanation of the relationship between said sequences and the instant invention is disclosed, as consideration of millions of sequences at once is impractical.

Withdrawn Rejections and Objections

7. The following rejections and objections made in the previous office action are withdrawn:

A. The rejection of claim 28 under 35 USC 112, second paragraph, is withdrawn in light of the amendment.

B. The rejection of claim 27 under 35 USC 102(b) over Ilag is withdrawn. The claim now requires that the agent comprises a PTD domain. Ilag does not teach agents which comprise PTD domains.

Rejections and Objections Maintained and Necessitated by Amendment

Claim Objections

8. Claim 28 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This objection is maintained for the reasons of record. Applicant argues on p. 5 of the remarks that the amendment to the claim is sufficient to overcome the objection, but the examiner disagrees. The claim now depends from claim 22, but the composition of claim 28 is the same as that of claim 22. Claim 28 does not further limit the parent claim; all that differs is a recited specific location related to an intended use.

9. Claim 21 is objected to because of the following informalities: it recites "wherein the agent comprises a PTD domain". To reflect more conventional claim language, it is recommended that the claim be amended to read "wherein the agent also comprises". This will clarify that the PTD domain is not part of the Pep5 polypeptide itself but is rather fused or conjugated to the polypeptide. Appropriate correction is required.

10. Claim 25 is objected to because of the following informalities: it is grammatically incorrect as it recites "... wherein the agent capable of inhibiting the p75 signal transduction pathway the action of inhibition...". Appropriate correction is required.

Priority

11. Applicant indicated, in the remarks filed 28 June 2006, that a translation will be submitted in the future. However, no translation has yet been made of record, so the effective filing date of all claims under examination remains 30 April 2003 for the reasons of record.

Claim Rejections - 35 USC § 112

12. Claims 21 – 22, 25 – 28, and 263 – 266 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

This rejection is maintained with respect to the previously presented claims and extended to the newly presented claims, which all ultimately depend from claim 21 or 27. The scope of independent claims 21 and 27 has been expanded considerably by applicant's amendment. Previously the claims were drawn to compositions comprising an agent in the p75 signal transduction pathway or an agent capable of specifically interacting with same. However, the claims now allow for inclusion of any "Pep5 polypeptide" comprising SEQ ID NO:2, or a sequence with "one or several amino acid substitutions, deletions, and additions which retains the biological activity of Pep5". The claims clearly allow for an unlimited number of additions and substitutions to the polypeptide to be administered. There is no upper limit on the length of the polypeptide to be administered, since the claims use the term "having", which is considered to be open claim language and akin to using the word "comprising". Furthermore, independent claims 21 and 27 both allow for "several" additions. The claims also allow for unlimited number of substitutions; the only requirement is that the polypeptide administered retain "the biological activity of Pep5".

It is important to note that the biological activity of Pep5 is not limited, either in the specification or the claim, to the ability to regenerate nerves. Applicant has specifically allowed for inclusion of many biological activities in the definitions provided. In US Patent Application Publication 2004/0191240, which is the publication of the instant disclosure, applicant states that "Examples of the biological activity of Pep5 include, but are not limited to, blocking of neurite outgrowth inhibition by a myelin derived protein." (see paragraph [0472]). Furthermore, paragraph [0531] provides a non-limiting definition of what a biological activity is; the paragraph states:

> As used herein, the term 'biological activity' refers to activity possessed by an agent (e.g. a polynucleotide, a protein etc.) with an organism, including activities exhibiting various functions (e.g. transcription promoting activity).

This definition is so broad as to be inclusive of any activity that a molecule may have when in an organism. Polypeptides have a plethora of functions, including those not dependent upon their specific amino acid sequence. For example, polypeptides can increase the osmolarity of a solution, thereby providing a driving force for the movement of solvent across a semi-permeable membrane. So taken together, the definition of 'biological activity' as set forth paragraphs [0472] and [0531] are clearly very broad.

Independent claims 21 and 27 require the composition comprise SEQ ID NO:2 or any variant that could be derived therefrom with any sequence, of any length, and with any activity in any organism. The specification does not describe which amino acid residues are required for the "biological activity". Given the breadth of the claims, the specification fails to disclose to the artisan that applicant was in possession of the invention now claimed, as it does not disclose a reasonable number of members of the genus of materials encompassed within the claim.

The claims are genus claims, because they encompass methods of administering a broad number of polypeptides so long as they a) either comprise or are derived from SEQ ID NO:2, with an unlimited number of possible additions, deletions, or substitutions and b) retain "biological activity" of Pep5. The specification describes only a single species falling within the genus, namely the protein of SEQ ID NO:2. The specification does not describe the full genus of proteins comprising SEQ ID NO:2 with unlimited possible additions deletions and substitutions.

Applicant is directed to the flow chart on p. 9 of the Revised Written Description Interim Guidelines Training Materials, available on the internet at <http://www.uspto.gov/web/offices/pac/writtendesc.pdf>, which is analogous to the instant situation. Claims 21 and 27 are genus claims, but neither the art nor the specification discloses a representative number of species falling within the genus. There is not even identification of any particular portion of the structure at the amino acid level that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

13. Claims 21 – 22, 25 – 28, and 263 – 266 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising the protein of SEQ ID NO:2 with or without a C-terminal alanine, does not reasonably provide enablement for compositions comprising any polypeptide sequence derived therefrom with an

infinite number of additions, deletions, and substitutions which retain the biological activity, as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is maintained with respect to the previously presented claims and extended to the newly presented claims, which all ultimately depend from claim 21 or 27. The scope of independent claims 21 and 27 has been expanded considerably by applicant's amendment. Previously the claims were drawn to compositions comprising an agent in the p75 signal transduction pathway or an agent capable of specifically interacting with same. However, the claims now allow for inclusion of any "Pep5 polypeptide" comprising SEQ ID NO:2, or a sequence with "one or several amino acid substitutions, deletions, and additions which retains the biological activity of Pep5". The claims clearly allow for an unlimited number of additions and substitutions to the polypeptide to be administered. There is no upper limit on the length of the polypeptide to be administered, since the claims use the term "having", which is considered to be open claim language and akin to using the word "comprising". Furthermore, independent claims 21 and 27 both allow for "several" additions. The claims also allow for unlimited number of substitutions; the only requirement is that the polypeptide administered retain "the biological activity of Pep5".

The definition of biological activity provided in the specification is very broad, and allows for the polypeptide to be administered to have any function in an organism, including for example modulating flow of water across a semipermeable membrane, or raising an antibody. The specification does not provide guidance to the artisan as to which amino acids must be retained in the resultant polypeptide such that "biological activity of Pep5" be retained. As stated above, the specification clearly considers the biological activity of Pep5 to be much broader than regeneration of nerves.

Even if the biological activity were limited to the regeneration of nerves, the specification still would not be enabling for the full scope of the claims. The specification does not provide guidance as to which amino acid sequences should be retained in the mutated sequence derived from SEQ ID NO:2 such that the nerve-regenerating activity will be retained. Random mutation of a protein sequence would be expected to yield inactive proteins.

Rudinger states on page 3 that "it is impossible to attach a unique significance to any residue in a [protein] sequence. A given amino acid will not by any means have the same

significance in different peptide sequences, or even in different positions of the same sequence". Rudinger further states on page 6 that "the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study". Thus in order to determine how to use the sequences derived from SEQ ID NO:2, the artisan would have to resort to painstaking experimentation. Given the breadth of the claims and the lack of guidance commensurate with their very broad scope, the degree of experimentation required would be undue.

Given the breadth of the claims, the fact that the specification shows a working example of administration of only polypeptides, i.e. that of SEQ ID NO:2 and of SEQ ID NO:2 with a C-terminal alanine, that actually regenerates nerves, a large amount of experimentation would be required to first determine how to make all possible polypeptides of unlimited length and unlimited biological activity. Because the specification does not provide guidance commensurate with the scope of claims 21 and 27, the large degree of experimentation required by the skilled artisan would clearly be undue. The remaining claims are rejected because they depend from a rejected base claim and fail to limit the claimed invention to enabled embodiments.

Claim Rejections - 35 USC §§ 102 and 103

14. Claims 21 – 22, 25 – 28 and 263 – 266 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Bredesen (US Patent Application Publication 2004/0192889, published 30 September 2004, filed 29 March 2002, claiming benefit of provisional applications filed 29 March and 2 April 2001).

This rejection is maintained for the reasons of record with respect to claims 21 – 22 and 25 – 28, and extended to new claims 263 – 266 for the reasons explained below.

Bredesen teaches the first helix of the intracellular domain of the p75 receptor fused to TAT protein (see p. 10, paragraph [0083]). TAT protein has a PTD domain, and the sequence of the intracellular domain of p75 can be derived from that of SEQ ID NO:2 with one or more additions, deletions, or substitutions. There is no upper limit on the number of changes that can be made to the sequence; the only requirement is that the resultant protein retain "the biological activity of Pep5". As set forth above, the definitions of "biological activity" provided by applicant are so broad as to include any function when administered to an organism. Both SEQ ID NO:2

and the intracellular domain of p75 receptor are capable of interacting with components of the p75 pathway and therefore the prior art product has "the biological activity of Pep5" as recited in claims 21 and 27. Thus the protein from Bredesen teaches all the structural elements of claims 21 and 27. Bredensen teaches that the protein is suitable for administration to cells, which meets the "suitable for in vivo or in vitro" limitation of claim 27. As Bredesen teaches the protein is suitable for administration to cells, it is in a form appropriate for delivery to a neuron at a site desired for regeneration and thus meets the limitation of claim 22. As claim 28 does not limit claim 21, it is rejected for the same reasons the parent claim is rejected.

The USPTO does not have the resources to determine if the prior art product is is able to sufficient to accomplish the inhibition, conversion, maintenance, or enhancement as recited in claim 25 or the suppression, extinguishing, or inhibition as recited in claim 26. However rejections under 102/103 are appropriate when the prior art teaches a product that appears identical to the claimed product except that it is silent as to an inherent property. In this case, the prior art product anticipates the claimed product, but the reference is silent as to whether or not the product is "capable of" performing certain intracellular functions. Note that the claim does not actually require that the product have this ability, but rather that it be merely capable of doing so. See MPEP § 2112(III).

Claim 263 is drawn to a kit comprising the composition of claims 21 or 27 and further comprising instructions. The recitation of nonfunctional printed matter does not distinguish the product from the prior art; see MPEP § 2112.01(III). Claim 264 is rejected as it requires no elements other than those set forth in claims 21 or 27. Claims 265 and 266 are rejected because the reference by Bredensen teaches administration of the polypeptides to cells (p. 10, paragraph [0083]), and this is done by contacting the cell-containing media with a solution as recited in claim 266. Claim 266 depends from claim 265, and as the prior art anticipates claim 266 it must anticipate claim 265 as well.

Applicant argues that the rejection over Bredensen should be withdrawn as the reference does not teach a composition comprising a Pep5 polypeptide. However, given the breadth of the definition of such polypeptides in the specification and the claims, which allow for unlimited additions, deletions, and substitutions, the reference does in fact teach a "Pep5 polypeptide".

15. Claims 21 – 22, 25 – 28, and 263 – 266 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ilag in view of Schwarze (1999. Science 285:1569 – 1572), Voet (Biochemistry, Second Edition, 1995. pp. 58 – 59), and Bertin (U.S. Patent Application Publication 2002/0061833, published 23 May 2002, filed 26 December 2000).

This rejection is maintained for the reasons of record and extended to the new claims as set forth below. Briefly, Ilag teaches the protein of SEQ ID NO:2 and teaches it binds to the intracellular domain of p75. Schwarze teaches fusion proteins comprising PTD domains, specifically the PTD domain from HIV TAT protein and teaches the method is applicable for delivery of any protein. Schwarze even demonstrates the utility of the method in delivering beta-galactosidase, a marker protein, to the brain. Schwarze also teaches that molecules larger than 600 daltons do not enter cells.

The reasons why the prior art references meet the limitations of claims 21 – 22 and 25 – 28 are set forth in the previous office actions and for the sake of brevity will not be repeated herein. Claim 263 comprises a kit, which requires the inclusion of non-patentable printed material; the recitation of nonfunctional printed matter does not distinguish the product from the prior art; see MPEP § 2112.01(III). Claim 264 is rejected as it requires no elements other than those set forth in claims 21 or 27. Claims 265 and 266 are rejected because the reference by Ilag teaches composition in a solution, which is on point to claim 266. Claim 266 depends from claim 265, and as the prior art renders obvious claim 266 it must render obvious claim 265 as well.

It would have been obvious to one of ordinary skill in the art to modify the protein sequence of SEQ ID NO:2 from Ilag et al. by fusing it to the TAT PTD domain, as taught by Schwarze. The motivation to do so is provided by Bertin, is to aid in crossing the cell membrane thereby inhibiting cell death, as Bertin teaches that proteins which bind to the intracellular domain of p75 inhibit cell death. Voet provides the weight of all twenty amino acids that are used in proteins and provides evidence that the protein of SEQ ID NO:2 (i.e. the protein from Ilag) is too large to enter the cell, thereby motivating the artisan to modify the protein from Ilag to allow it to enter cells.

Applicant argues that attaching the PTD domain might alter the function of the protein from SEQ ID NO:2 and thus constitutes a "try and see" approach. Applicant's arguments have been fully considered but they are not persuasive. The reference by Schwarze makes no mention of why it would not be reasonable to expect success when attaching the PTD domain to

any protein, or of any reason to believe any protein would become inactive after said attachment. Quite to the contrary, Schwarze teaches the method is useful for delivery of proteins into cells in general, and specifically teaches it is useful for delivering an enzyme to the neurons of the brain. Note that the staining pattern observed in the brain after delivery of the beta-galactosidase enzyme indicates that this protein retains its activity after being fused to the PTD domain and brought into cells.

Conclusion

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DK

Daniel E. Kolker, Ph.D.
September 7, 2006

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER